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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,463	12/06/2001	Luis Enrique Fernandez Molina	024518-00001	4352

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,463	MOLINA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 21-28* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/6/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Restriction mailed 4/12/05 is hereby vacated and a new restriction is set forth below.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, 27 and 28, drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, classified in class 530, subclass 350.

II. Claims 21 and 22, drawn to a method of treating cancer in a patient comprising administering to said patient an anticancer effective amount of a composition of claim 1, classified in class 514, subclass 2.

III. Claim 23, drawn to a method of treating viral or bacterial infections comprising administering to said patient an anti-infection effective amount of a composition of claim 1, classified in class 514, subclass 2.

IV. Claim 24, drawn to a method for treating an auto-immune disease in a patient comprising administering to said patient an anti-autoimmune disease effective amount of a composition of claim 1, classified in class 514, subclass 2.

V. Claim 25, drawn to a method for treating a non-transmissible chronic disease in a patient comprising administering to said patient an anti non-transmissible chronic disease effective amount of a composition of claim 1, classified in class 514, subclass 2.

VI. Claim 26, drawn to a method for treating a AIDS in a patient comprising administering to said patient an anti-AIDS effective amount of a composition of claim 1, classified in class 514, subclass 2.

2. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups II-VI are materially distinct methods which differ at least in method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. For example, each Group is drawn to the treatment of etiologically and functionally different diseases and to the treatment of different populations of patients that have the specific disease being treated. Each of the groups employs chemically distinct reagents to accomplish the objective that comprise treating different populations using different method steps, and/or dosages, and/or schedules

used, response variables, and criteria for success. Searching all of the groups with all of the different variables would invoke a high burden of search.

Inventions I and II-VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition of Group I can be used to generate antibodies or for affinity chromatography.

Because these inventions are distinct for the reasons given above and the search required for one Group is not required for any other Group, and because some Groups have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Note:

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.

Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

SPECIES ELECTION for GROUP I

3. Applicant must elect a species from each of A-C below:

A. This application contains claims directed to the following patentably distinct **immunogenic antigen** species (claim 2): **peptides, polypeptides, proteins, or their corresponding nucleic acid sequences, target cells with vaccine interest, lysate, or specific combination**. The species are independent or distinct because each antigen is structurally and functionally distinct.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

B. This application contains claims directed to the following patentably distinct **growth factor receptor** species (claim 5): **HER-1, HER-2, or PDGR-R**. The species

are independent or distinct because each receptor is structurally and functionally distinct.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

C. This application contains claims directed to the following patentably distinct **adjuvant** species: **oily adjuvant (claims 9-11) or polypeptide (claims 9, 12, and 13)**. The species are independent or distinct because each adjuvant is structurally and functionally distinct.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

4. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. During a telephone conversation with Jeffrey Ihnen on 4/3/06, a provisional election was made to prosecute the invention of Group I, amended claims 1-13, 27 and 28 from the amendment mailed 1/2/06. Applicant elected the species: polypeptide (claim 2), HER-1 (claim 5), and oily adjuvant (claims 9-11). **Affirmation of this election must be made by applicant in replying to this Office action**

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Claims 1-13 and 21-28 are pending. Claims 14-20 are canceled. During a telephone conversation with Jeffrey Ihnen on 4/3/06, Examiner offered to simplify the restriction to four groups, as opposed to 67 groups, as previously restricted by another Examiner. Examiner also asked for an election of a Group and species, rather than send a second non-compliant letter for failing to elect a species from the previous restriction. Mr. Ihnen requested a new restriction of the amended claims mailed 1/2/06 and elected Group I, claims 1-13, 27 and 28 and the species: polypeptide (claim 2), HER-1 (claim 5), and oily adjuvant (claims 9-11), as stated above in section 5. Claims

21-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 12 and 13 are withdrawn from consideration as being drawn to non-elected species.

Claims 1-11, 27 and 28 are currently under prosecution.

Specification

7. The disclosure is objected to because of the following informalities: In the drawings, Figure 5 has an X-axis label written in Spanish: "Dia" should be "Day". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites the limitation "**the adjuvant**". There is insufficient antecedent basis for this limitation in the claim because there is no adjuvant recited in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-10, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,788,985, Rodriguez et al., issued 8/4/98 (IDS), in view of US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64).

The claims are drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC (claim 1), wherein the low immunogenic antigen is a polypeptide (claim 2), wherein the low immunogenic antigen is a growth factor receptor (claim 3), wherein the extra cellular domains of the growth factor receptor may or may not contain the trans-membrane region (claim 4), wherein the growth factor receptor is HER-1 (claim 5), wherein the *Neisseria meningitides* is either a wild type or genetically modified strain (claim 6), wherein the VSSPs are obtained by hydrophobically incorporating the gangliosides into the OMPC (claim 7), wherein the gangliosides are GM3 or their N-glycosylated variations (claims 8 and 28), wherein the adjuvant is an oily adjuvant and is Incomplete Freund's Adjuvant (claims 9 and 10), and wherein the composition further comprises one or more adjuvants (claim 27).

US Patent 5,788,985 teaches a pharmaceutical composition that potentiates the immunogenicity of low immunogenic antigens comprising an Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC (Examples 2-4). US Patent 5,788,985 teaches that the pharmaceutical composition increases the immune response against N-glycolsylated ganglioside, especially N-glycol GM3 (NGcGM3) which can be used for the treatment of cancer (col. 1, lines 1-12), especially breast cancer which has a higher expression of gangliosides GM3 and GD3 compared to normal breast tissue (abstract; col. 1, lines 59-63 and Example 6), hence gangliosides are targets in treatment approaches (col. 1, lines 64-66). US Patent 5,788,985 teaches the incorporation of gangliosides, including the hydrophobic incorporation of NGcGM3, into the OMPC (col. 2, lines 30-36; col. 3, lines 1-20; Example 2), wherein the OMPC would be expected to be either a wild-type or a genetically modified strain (col. 6, lines 1-3).

US Patent 5,788,985 does not teach the pharmaceutical composition further comprising the low immunogenic antigen HER-1 or Incomplete Freund's adjuvant.

US Patent 4,857,637 teaches a pharmaceutical composition comprising the polypeptide epidermal growth factor receptor (EGFR, or HER-1) as an antigen to immunize animals against the EGFR (col. 3, lines 36-43; col. 4, lines 58-63). US Patent 4,857,637 teaches that EGFR is overexpressed in malignant cells and is a desirable target for therapy (col. 3, lines 63-66; col. 4, lines 26-38). Immunization may comprise administering growth factor receptor derivatives or intact receptors (col. 4, lines 57-61). Growth factor receptors comprise extracellular, transmembrane and cytoplasmic

domains, wherein immunization of a receptor comprising the extracellular domain is desirable because the extracellular domain is accessible to antibodies under *in vivo* conditions, unlike the intracellular or cytoplasmic domains (col. 8, lines 47-68). US Patent 4,857,637 teaches the immunization of growth factor receptors with an adjuvant, such as Incomplete Freund's, because poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants (col. 4, lines 63-68; col. 5, lines 50-55; col. 7, lines 1-3; col. 18, lines 50-55).

Udayachander et al teach that many malignancies, such as breast cancer, overexpress EGFR and EGFR is a target for therapy (abstract).

These references suggest the importance of each of the claimed pharmaceutical composition components in stimulating an immune response to the ganglioside or EGFR antigen. However, the references are deficient in that they do not teach using these components together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein ganglioside antigens have been incorporated into the OMPC taught by US Patent 5,788,985 and the EGFR (HER-1) antigen taught by US Patent 4,857,637 in combination in order to treat malignant tumors that overexpress these two antigens, such as breast cancer, because US Patent 5,788,985 teaches that breast cancer overexpresses ganglioside GM3 and Udayachander et al teach that breast cancer overexpresses HER-1. One of ordinary skill in the art would have been motivated to use the two pharmaceutical components in combination in a method of treating a malignant tumor that overexpresses the two

antigens, such as breast cancer, in view of the importance of targeting these two antigens for cancer therapy. Each of these agents had been taught by the prior art to be therapeutic targets in the treatment of malignant tumors, such as breast cancer, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. One of ordinary skill in the art would have reasonably expected to obtain effective therapeutic targeting of malignant tumors, such as breast cancer, with either or both of these agents since both had been demonstrated in the prior art to successfully illicit an immune response specific to the target cancer antigen.

Similarly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Incomplete Freund's adjuvant in addition to the two pharmaceutical components because adjuvant is conventionally used in pharmaceutical compositions and US Patent 4,857,637 teaches that poorly immunogenic proteins are rendered more immunogenic by the use of adjuvants such as Freund's Incomplete. One would have been motivated to add Freund's Incomplete to the pharmaceutical composition taught by the combined references in order to boost the immune response to the antigens for therapeutic purposes.

10. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,788,985, Rodriguez et al., issued 8/4/98 (IDS), US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64), in further view of Carr et al (Melanoma Research, June 2001, 11:219-227).

The claim is drawn to the composition of claim 10 wherein the Incomplete Freund's adjuvant is Montanide ISA 51.

US Patent 5,788,985, Rodriguez et al., issued 8/4/98, US Patent 4,857,637, Hammonds et al., issued 8/15/89 and Udayachander et al (Human Antibodies, 1997, 8:60-64) teach a pharmaceutical composition as set forth above. The combined references do not teach the Incomplete Freund's adjuvant is Montanide ISA 51.

Carr et al teach a pharmaceutical composition comprising Montanide ISA 51 and a very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein GM3 gangliosides have been incorporated into the OMPC. Carr et al teach the significant increase in overall survival of mice inoculated with cancer cells expressing gangliosides after administration of this pharmaceutical composition (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the Incomplete Freund's adjuvant Montanide ISA 51 with the pharmaceutical composition taught by the combined references because the combined references teach the use of Incomplete Freund's adjuvant to increase immunogenicity of antigens and Carr et al teach the use of Incomplete Freund's adjuvant Montanide ISA 51 specifically as a form of Freund's adjuvant in

combination with the VSSP that successfully treated mice. One would have been motivated to use Montanide ISA 51 as a form of Freund's adjuvant in combination with the VSSP/HER-1 composition because of its demonstrated success in the lab of increasing the survival of mice with cancer expressing gangliosides.

11. **Conclusion:** No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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